## REMARKS

The specification has been amended to update the status of the priority application. Claims 1-43 and 49-50 stand cancelled. Claims 43-48, 51-54 and 57 have been amended. New claims 58 to 63 have been added. No new matter has been added by virtue of these amendments; support therefore being found throughout the specification and in the original claims of the application.

**Rejection under 35 USC §112, second paragraph**

Claims 43, 46-48 and 51-54 stand rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctively claim the subject matter which applicant regards as the invention.

The Examiner states that claim 43 is indefinite as it is unclear if the claimed method uses only a compound of formula I, or a combination of a phosphodiesterase (PDE) isoenzyme inhibitor, and/or a bronchodilator, and a compound of formula I.

While the claim language is believed to be clearly understood when read in view of the supporting specification, claim 43 has been amended for additional clarity. In particular, claim 43 has been amended to recite that the disease is characterized by being amenable to treatment with a phosphodiesterase (PDE) isoenzyme inhibitor and/or a bronchodilator. This amendment does not alter the scope of the claim. As amended, the claim is definite and distinctly points out that the method of the claim does not require administration of the compounds of the claim with other compounds, pharmaceutically active or otherwise; however, the claim does not preclude administration of the compound with other compounds.

Claims 46-48, 51 and 52 are rejected as being dependent on claim 43, thereby reciting the allegedly indefinite method. As claim 43 is now definite, claims 46-48, 51 and 52 are also now definite and allowable.

The Examiner states that claim 53 is indefinite as it is unclear what diseases are included in the group of diseases in which increasing intracellular concentration of cAMP is considered beneficial. Applicant submits that the action of cAMP within cells is well characterized, as demonstrated in the specification on page 1, lines 17-28:

> In a disease such as asthma, the principal cells involved in the associated bronchoconstriction and inflammatory processes are subject to inhibitory control by cAMP. Inhibitors of type III phosphodiesterase raise intracellular levels of cAMP, leading to relaxation of bronchial smooth muscle, whereas inhibitors of type IV phosphodiesterase inhibit the release of damaging mediators from pro-inflammatory cells. Thus, in principle, a combined PDE III/V inhibitor should have the desirable effects of a β-adrenoceptor agonist plus an inhaled anti-inflammatory steroid which are currently the mainstay of treatment in severe asthma. Moreover, a combined PDE III/IV inhibitor given by inhalation should achieve beneficial effects similar to a β-agonist plus inhaled steroid and should be an unusually effective treatment of asthma and other respiratory disorders without the undesirable glucocorticoid effects of the steroid such as osteoporosis and the stunting of growth.

Applicant submits that even in the absence of presenting an exhaustive list of diseases, one skilled in the art can readily determine if a subject is in need of a smooth muscle relaxant, such as an inhibitor of type III phosphodiesterase, for the treatment of a disease. Similarly, one skilled in the art can readily determine if a subject is in need of an anti-inflammatory agent, such as an inhibitor of type IV phosphodiesterase, for the treatment of a disease.

Additionally, in an effort to expedite allowance of the application, claim 53 has been amended as set forth above to recite these characteristic activities of type III and type IV phosphodiesterase inhibitors. Applicant submits that the amendment does not alter the scope of the claim.

The compounds of the invention act as smooth muscle relaxants. The compounds of the invention have been demonstrated to inhibit electrical-induced contraction of guinea pig tracheal smooth muscle (Example A); to protect against histamine induced bronchospasm upon exposure of the lungs to dry powder (Example E1); and to reduce mean arterial blood pressure in mice upon intravenous

administration (Example E2). These data demonstrate the ability of the compounds to act as smooth muscle relaxants in both prophylactic and acute treatment models.

The compounds of the invention also act as anti-inflammatory agents. The compounds have been demonstrated to act as an anti-inflammatory agent, inhibiting LPS induced TNF-α release from monocytes (Example D); and to prevent eosinophil infiltration in response to allergen challenge in a guinea pig model of antigen-induced eosinophilia (Example E). These data demonstrate the ability of the compounds to act as anti-inflammatory agents in both prophylaxis and treatment models. Applicant submits that claim 53 is definite and particularly points out the subject matter to be claimed.

Applicant respectfully submits that the within amendments obviate the rejection under 35 USC §112, second paragraph. Withdrawal of the rejection is therefore requested.

**Rejection under 35 USC §112, first paragraph**

Claims 43-48, 51 and 52 stand rejected under USC 35 §112, on the grounds of enablement (for prevention) and scope of enablement (for diseases). The position is taken that the claims contain subject matter, which allegedly was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to, to make and/or use the invention.

The Examiner states that the recitation of claims 43-45 of a "method for the ... prophylactic treatment" does not have enablement in terms of patient profile, and that without such a protocol, a skilled clinician would have to carry out undue experimentation to use the claimed compound in any specific disease. The Examiner further states that as many of the diseases listed in the application are chronic diseases, it would not be possible to treat them in a prophylactic manner. Applicant respectfully disagrees.

Applicant submits that determination of an appropriate dose is within the realm of "routine experimentation" in the art. The matter is discussed further below in regard to the scope of enablement.

As discussed in the response filed on February 24, 2006, as is often the case, individuals who suffer from chronic diseases experience asymptomatic periods. Thus, although the individual may not be suffering an 'outbreak', e.g., exhibiting symptoms of the disease at any given time, the individual nonetheless remains susceptible to and at risk for repeated occurrences of the disease. Methods of the invention would be suitable for administration to such individuals in a prophylactic manner in order to avoid repeated outbreaks and mitigate the chronic effects of the diseases.

Moreover, as stated by the Examiner discrete activities or lifestyle choices can predict future disease. Some are well known. Exposure to certain pollutants, such as those encountered under occupational conditions, can result in asthma. Smoking can result in COPD. Some are less well known. Sensitization to cat allergen is associated with asthma in older men and predicts new-onset airway hyperresponsiveness (see, Litonjua et al, *Am. J. Respir. Crit. Care Med.* **156**:23-27, 1997, copy enclosed). Infantile wheeze can be a predictor of childhood asthma (see, Marguet et al., *Am. J. Repir. Crit. Care Med.* **159:**1533-1540, 1999, copy enclosed). Therefore, although asthma and COPD are chronic diseases, their development can sometimes be anticipated.

As all of these diseases, or exacerbations of these diseases, are preceded by inflammation. An inhibitor of inflammation, such as the compounds of the invention, would likely be useful in the prevention of the diseases. This conclusion is supported by the data of Example E that show that a compound of the invention was able to prevent bronchospasm and eosinophil infiltration in response to administration of an pulmonary insult. Therefore the compounds of the invention can be used for the prophylactic treatment of disease and the claims are enabled.

Nonetheless, the claims have been amended to remove the "prophylactic" aspect of the invention, merely to expedite allowance of the application.

The Examiner has further rejected the claims for not reasonably providing enablement for the treatment of diseases beyond allergic asthma, allergic rhinitis, hay fever, or atopic dermatitis. The Office Action states that the specification does not provide enablement for the treatment of other diseases "*allegedly* related to PDE III or PDE IV such as: asthma, bronchitis, COPD, ARDS, cystic fibrosis, psoriasis, ocular inflammation, cerebral ischemia, or autoimmune diseases in which increasing intracellular concentration of cAMP is considered beneficial" (see pg. 5, emphasis added).

In the Office Action, the Examiner cites paragraph 0114 of the specification that lists these diseases "in which raising the intracellular concentration of cAMP is desirable," demonstrating the Examiner is aware of support for the claim language in the text.

In regard to claim 43, the Office Action states that the phrase "any other disease including... in which increasing intracellular concentration of cAMP is considered beneficial" covers diseases that have yet to be discovered and is overly broad. The language appears in the specification, but is not recited in present claim 43. If the intention was to reject the language recited in the instant claim 43 which now includes "treatment of a disease in a mammal, wherein the disease is characterized by being amenable to treatment with a phosphodiesterase isoenzyme inhibitor and/or a bronchodilator," Applicant respectfully traverses. The actions of phosphodiesterase isoenzyme inhibitor and/or a bronchodilator are well known, and they are widely used in the art for the treatment of disease. Therefore, diseases, and symptoms thereof, amenable to treatment with such compounds are well known to those skilled in the art.

The Examiner states that claims 44 and 45 do not have an unduly broad scope, but are allegedly not enabled in terms of the bioassays done; and that claims 46-48, 51 and 52 are either allegedly unduly broad or not enabled methods.

The Office Action further states that claim 53, like claim 43, covers a myriad number of diseases and is allegedly unduly broad. Claim 54 is also alleged to be unduly broad, and claims 55 to 57 are alleged to be non-enabled. Applicant respectfully traverses the rejections.

*In re Wands* (citations omitted) is cited for factors to be considered in determining the appropriate scope of the claims. The Office Action states that the amount of direction or guidance presented in the specification is insufficient. The Office Action states that one *in vitro* assay of the inhibition of PDE III and PDE IV isoenzymes, and one *in vivo* assay of histamine induced bronchospasm are provided. Applicant directs attention to Example E that provides two additional *in vivo* tests not acknowledged in the Office Action. Example E2 shows that the compound of the invention had a dose dependent effect on mean arterial blood pressure in guinea pigs. Example E3 shows that the compound of the invention had an effect on antigen-induced eosinophilia in the ovalbumin sensitized guinea-pig, a model commonly used for the study of asthma and airway hyperresponsiveness (see, e.g., Wang et al., *J. Clin. Invest.* **102:**1132-1141, 1998; Keane-Myers et al., *J. Immunol.* **160**:1036-1043, 1998, copies enclosed). Example D shows inhibition of LPS induced TNF-α release from monocytes. Lipopolysaccharide (LPS), a purified derivative of endotoxin, is related to several occupational pulmonary diseases and to severe domestic asthma. Inhalation of pure LPS produces both a systemic and a bronchial inflammatory response, providing a non-allergic response to a pulmonary inflammatory mediator (see, e.g., Michel, *Am. J. Respir. Crit. Care Med.* **156:**1157-1164, 1997, copy enclosed), providing support for the use of the compounds of the invention for treatment of both allergic and non-allergic inflammatory diseases or conditions. In Example A, six different compounds of the invention were demonstrated to inhibit electrical-induced contraction of guinea pig tracheal smooth muscle. Applicant submits that this variety of assays, combined with

the knowledge of those skilled in the art, provide sufficient direction and guidance regarding evaluation of compounds of the invention.

The Office Action takes the position that the state of the prior art does not suggest the methods of the invention based on the activity of the most closely related chemical compound. The Examiner states that the core of 3, 4, 6, 7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one is known to treat cardiovascular disorders, particularly hypertension (i.e., high blood pressure) (see p. 8). Applicant notes that in Example E2, a compound of the invention was demonstrated to decrease mean arterial blood pressure, demonstrating that at least some of the activities of the compounds of the invention can be predicted based on structure. Moreover, Applicant submits that the activity of a structurally similar compound is only a narrow view of what is known in the art. Applicant submits that the prior art includes many assays, such as those taught by the specification, and the action of various phosphodiesterase isoforms and inhibitors.

The Examiner states that despite the high level skill of those skilled in the art, that experimentation would be required. Applicant submits that those skilled in the art would know what experiments would need to be done, such as those provided by the Office Action, including determination of $IC_{50}$ and $LD_{50}$ values. Applicant submits that effort, time, and resource are not a consideration relevant to the level of skill in the art. Moreover, research in the biomedical arts typically requires effort, time, and resources, even when the research is routine.

The Examiner states that the unpredictability in the art is high, and the quantity of experimentation required is undue. Applicant respectfully disagrees. Applicant submit that what is an ordinary amount of experimentation in the art of the instant application must be considered in the analysis of what constitutes "undue experimentation." *In re Wands* states:

> The determination of what constitutes undue experimentation in a given case requires application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v.*

> *Uniroyal, Inc.* (citation omitted). The test is not merely quantitative because a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. (pg. 1404)

Applicant submits that the experimentation required to identify specific phosphodiesterase inhibitors useful in the methods of the invention is routine, and the specification provides substantial guidance with respect to the direction in which experimentation should proceed. Similarly, determining appropriate dosage is routine experimentation in the art (see, e.g., Example E2 reports a dose dependent effect of a compound of the invention).

The invention of the instant application includes the discovery of a class of compounds that act as type III and type IV phosphodiesterase inhibitors.. Based on this discovery, one skilled in the art can readily make use of known compounds in known assays to determine the specific compounds that can be used for the methods of the invention. Applicant submits that the specification provides a number of compounds, and methods by which to test them, such as those provided in Examples A to E. Applicant submits that animal testing does not constitute undue experimentation. The methods used for analysis of the phosphodiesterase inhibitors in the specification were not developed by the inventors of the instant application, but instead are part of routine experimentation within the art.

The Examiner seems to suggest that in order for the claim to be enabled, it is necessary for all of the compounds to be predictably active in the claimed methods. Applicant respectfully disagrees. *In re Wands* teaches that a limited level of success, so long as there is some success, is sufficient to meet the enablement requirement.

During prosecution, *Wands* submitted a declaration under 37 C.F.R. §1.132 providing information about all of the hybridomas that Appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybridomas. The next six fusion experiments all produced hybridomas.

Of all of the fusion experiments performed by Wands, only four of the nine fully characterized hybridomas produced antibodies that fell within the scope of the claims. Wands did not teach an improved method for making hybridomas. Wands taught and claimed a method that required the use of hybridomas having specific claimed characteristics. An additional 134 hybridoma lines were frozen and stored without further analysis. The number of these hybridomas that produce antibodies that fall within the limitations of the claims is unknown.

*Wands* demonstrates that routine experimentation is not always trivial or successful, and that uncertainty in regard to result is tolerable within the scope of enablement. If the experimental path and data analysis have sufficient certainty (i.e., are routine), the claims are enabled. Not all outcomes from routine experimentation need to fall within the scope of the claims to meet the requirement of enablement.

Applicant respectfully submits that the requirements of 35 USC 112, 1st paragraph, do not necessitate an encyclopedic recounting of all known or yet to be discovered diseases or conditions that might be claimed or used in the method of the invention when a generic description is provided. Applicant has provided both a generic description and a list of diseases and/or conditions to be treated with the compounds of the invention. The existence of a class of compounds known as phosphodiesterase inhibitors clearly demonstrates that those skilled in the art can recognize such compounds when they are in possession of same.

Applicant's arguments are strongly supported by recent Federal Circuit decisions. For example, in *Union Oil Co. v. Atlantic Richfield Co. 208 F.3d 989,997* (Fed. Cir. 2000), the court concluded, "A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language." In accordance with this conclusion, Applicant provides explicit examples of conditions and diseases to be treated with the compounds of the invention.

Applicant respectfully submits that the within amendments obviate the rejection under 35 USC §112, first paragraph. Withdrawal of the rejection is therefore requested.

In view of the above amendments and remarks, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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Appendix follows: 5 references